EFFECTS OF NEURODYNAMIC MOBILIZATION ON SENSORY SYMPTOMS AND NERVE FUNCTIONS IN PAINFUL DIABETIC PERIPHERAL NEUROPATHY

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Certificate

I hereby declare that the short synopsis " Effect of Neurodynamic mobilization on sensory symptoms and nerve functions in Painful Diabetic Peripheral neuropathy" being submitted in partial fulfillment of the requirement for the degree of Doctor of Philosophy in Physiotherapy under faculty of Allied Health Sciences of Manav Rachna International Institute of Research & Studies, Faridabad during the academic year 2021-2022

It is a bona fide record of original work carried out under the supervision of Dr. Irshad Ahmad / Dr.Arun kumar chandresh singh and has not been submitted in full or part to any other university or institute for degree or diploma. Further, it is certified that short synopsis is plagiarism free and proof has been submitted.

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ABSTRACT

Background/Introduction: Painful Diabetic peripheral neuropathy is a chronic complication of diabetes mellitus. Chronic hyperglycaemia and microangiopathy causes biomechanical changes in peripheral nerves resulting in neuropathic pain and altered sensory functions. Quality of life is impaired in such cases due to reduced mobility, sleep disturbances, reduced social participation and anxiety.

Objectives: The objective of this research is to envision the impact of Neurodynamic mobilization on sensory symptoms and nerve functions in Painful diabetic Peripheral neuropathy and to compare the same with established physiotherapy management in treatment of Painful Diabetic Peripheral neuropathy (PDPN).

Methodology: It will be a Randomised Controlled trial having one control group and two experimental groups. Total of 96 subjects will be chosen as per inclusion/exclusion criteria. These subjects would then be distributed on random basis to any one of three groups (n=32). Outcome measures will be Nerve conduction studies, Quantitative sensory testing, Ankle Proprioception, Pain, Quality of life, psychological status and Neuropathy disability score. Neurodynamic mobilization and foot exercises will be given to group A, Transcutaneous electrical nerve stimulation (TENS) and foot exercises will be given to group B and only foot exercises will be given to group C (Control group). All three groups will also receive education regarding glycaemic control and foot care.

Expected Outcome: Experimental group A and Group B both are expected to be more effective than control group in management of Pain and other sensory symptoms in patients with PDPN.

Key words: Painful Diabetic Peripheral neuropathy, Neurodynamic mobilization, physiotherapy in diabetic neuropathy, Foot exercises in Diabetic neuropathy.

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1. Introduction

1.1 Definition, Clinical presentation and prevalence of PDPN

The International Diabetes Federation estimates 537 million adults with diabetes in the age group of 20 to 79 years. Further this is assumed to upsurge to 783 million by 2045 (IDF Diabetes Atlas,2021). Diabetes is a life-threatening disease and has caused 6.7 million deaths worldwide. It is a metabolic disorder that causes systemic damage resulting in musculoskeletal and neuropathic complications. Diabetic peripheral neuropathy (DPN) is one such complication that occurs in 30% to 50% of population with diabetes. DPN is described as a "chronic, symmetrical, length dependent sensorimotor polyneuropathy" presenting as Pain, dysesthesias, motor dysfunctions and impaired quality of life (Allen et al., 2016; Petersen et al., 2021). Amongst these Patients around 18% develops chronic neuropathic pain, body dysfunctions, sleep disturbances, anxiety and fatigue called as Painful Diabetic peripheral neuropathy (Spallone & Greco, 2013). As per International Association for the Study of Pain, PDPN is defined as "pain arising as a direct consequence of abnormalities in the peripheral somatosensory system in people with diabetes"(Tesfaye et al., 2010).

Though to estimate prevalence of PDPN is difficult (Tesfaye et al., 2010) several studies has reported it to range from 23.3% to 26.4% (Davies et al., 2006; Kiyani et al., 2020). The risk factors for neuropathic progression of disease includes age, hypertension, obesity, dyslipidaemia, tobacco intake and impaired glucose control (Cade, 2008). The severity of symptoms is related with diabetes duration and glycaemic control (Davies et al., 2006; Snyder et al., 2016) with greater prevalence in female gender (Abbott et al., 2011; Erbas et al., 2011; Jambart et al., 2011; Spallone & Greco, 2013).

Chronic neuropathic pain is most alarming symptom of PDPN and prompts patients to seek medical advice. This pain can be burning, prickling, stabbing, lancinating, shooting or cramping (Naderi Nabi et al., 2015; Peltier et al., 2014; Xiaohua et al., 2021). Other peculiar sensations experienced by patients of PDPN are allodynia, numbness and paraesthesia (Pai et al., 2021; Shillo et al., 2019). These sensations are constantly disabling in some cases that usually begins in toes and fingers, later involving both lower limbs and gradually extending to upper limbs in a glove and stocking pattern (Allen et al., 2016; Yovera-Aldana et al., 2021). Further, progression of disease results in decline in skeletal muscle functions that reduces mobility, impairs balance (Jamal et al.,

2020; Timar et al., 2016) and predisposes to delayed healing (Ahmed, 2005), chronic infections, recurrent falls and amputations (Booya et al., 2005; Jamal et al., 2020; Parasoglou et al., 2017). Constant pain and other unpleasant sensations in PDPN interferes with sleep leads to reduced mobility, recreational activities and social participation that causes anxiety, depression and negatively affects quality of life (Galer et al., 2000; Gore et al., 2006; Jamal et al., 2020; Parasoglou et al., 2017).

1.2 DPN and PDPN

DPN is the result of structural and functional changes in peripheral nerves caused by altered metabolism and microvasculature inevitable due to hyperglycaemia, dyslipidaemia and altered insulin signalling (Rosenberger et al., 2020). Though only half of DPN population develops neuropathic pain and other sensory symptoms. The chronic pain in PDPN results from damage of afferent nociceptors leading to peripheral sensitization, hyper excitability of central neurons and spontaneous generation of nerve impulse (Kessler & Hong, 2013; Nee & Butler, 2006). Risk factors that can contribute to development of PDPN includes increased glycaemic burden (Themistocleous et al., 2016), increasing age (Van Acker et al., 2009), obesity (Ziegler et al., 2018), female gender (Truini et al., 2018) and specific genotype like mutations in voltage gated sodium channels (Hoeijmakers et al., 2015). Other factors responsible for the same are vitamin D deficiency (Blesneac et al., 2018), reduced vascular endothelial growth factor expression, intra epidermal nerve fibre loss (Quattrini et al., 2008) and increased levels of methylglyoxal that leads to formation of advanced glycation end products (Feldman et al., 2019) and activation of transient receptor potential channel ankyrin 1(TRP1) and sodium channel Nav 1.8 (Huang et al., 2016). Various changes in higher brain centres (Tesfaye et al., 2016) like cortical atrophy and reorganisation (Cauda et al., 2009), increased synaptic transmission in spinal cord (Feldman et al., 2019), reduced inhibition of descending pathways and altered blood flow in anterior cingulate cortex (Watanabe et al., 2018) are also hypothesized to be a cause of PDPN (Sloan et al., 2018).

1.3 Effect of PDPN on peripheral nerve

PDPN is a result of long term hyperglycaemia and metabolic disturbances which causes accumulation of sorbitol and fructose in nerves via increased polyol pathway, hexosamine pathway (Callaghan et al., 2012) and glycolysis resulting in mitochondrial dysfunction and oxidative stress in peripheral nerves (Feldman et al., 2019; Sloan et al., 2018; Yagihashi et al.,

2011). Hyperglycaemia and dyslipidaemia lead to Schwann cell stress by neuronal and microvascular damage that further causes reduced nerve conduction velocity and neuronal blood flow. Impaired cell signalling occurs due to accumulation of advanced glycation end products (Ahmed, 2005) diacylglycerol, protein kinase c activation and dysregulation of sodium channel (Yang et al., 2016). These changes interrupts axoplasmic flow causing endoneural hypoxia, fibrosis with consequent demyelination and degeneration of peripheral nerves that alters nerve biomechanics (Cade, 2008; Da Silva et al., 2015; Hernández-Secorún et al., 2021; Tesfaye et al., 2010).These changes results in neural lesions in short as well as long fibers. Vascular insufficiency and neural ischaemia leads to increased concentrations of tumour necrosis factor alpha and interleukin beta around the nerves that sensitize nerve endings and causes mechanical hypersensitivity (Zhu et al., 2018).

All these changes affects nerve biomechanics by altering connective tissue structure and extracellular matrix of peripheral nerves thereby altering its conduction velocity (Boyd & Dilley, 2014). Depending upon duration and severity of hyperglycaemia in PDPN, changes in mechanical, thermal, vibration and perception pain thresholds can also be seen thus affecting its mechanosensitivity (Boyd et al., 2010).

1.4 Role of Neurodynamic mobilization in PDPN

Neurodynamic mobilization are graded mobilization techniques applied to peripheral nerves in which different combinations of limb and spine movements are used to correct the altered physiology of the concerned nerve. These techniques can cause movements of neuraxis, meninges, nerve roots and peripheral nerves (Shacklock, 1995) that helps to restore altered neurodynamics by maintaining the balance and smooth physiological motions between nerve and associated mechanical interfaces. This facilitates neural adherence and thus improves vascularity (Basson et al., 2017; Shacklock, 2008). It acts by limiting intraneural fluid accumulation through its intraneural and extraneural effects, thus restores altered mechanosensitivity of affected nerve and movement and functions of associated limb (Domingues, 2018). It also plays a crucial role in regeneration of affected neurons , promotes neuroplasticity and is considered as a safe treatment (Carta et al., 2021).

Neurodynamic mobilization techniques are known to restore normal mobility and elasticity of peripheral nerves by improving axonal regeneration due to increased formation of myelin protein

zero (MPZ) and neural growth factor (NGF) (Carta et al., 2021; Da Silva et al., 2015). The oscillations produced by these selective gliding and tensioning techniques reduces concentration of pro inflammatory mediators (Zhu et al., 2018)), alleviates Pain, facilitates nerve gliding, improves axoplasmic flow, reduces neural oedema and improves sensory functions of nerves (Shacklock, 1995). This reverses fibrosis that causes neural structural and functional compromise (Gilbert et al., 2015). Such techniques can alleviate pain and reduce disability associated with diabetes mellitus by addressing changes in mechanosensitivity of peripheral nerves (Boyd et al., 2017). Most recent literature has also shown that uniaxial tension applied in neurodynamic techniques are capable of promoting neurite outgrowth in sensory and motor neurons by upregulation of PIEZO1 gene expression (Carta et al., 2021).

Evidence based literature is available on effects of neurodynamic mobilization on neuropathic painful conditions like carpal tunnel syndrome (Bialosky et al., 2009; Talebi et al., 2018), cubital tunnel syndrome (Oskay et al., 2010), radial tunnel syndrome (Cleary, 2006), spinal radiculopathies (Efstathiou et al., 2015; Sharma & Sheth, 2017), non-radicular low back pain (Neto et al., 2017), lower extremity symptoms (George, 2002) and neuropathic pain in diabetes (Boyd et al., 2017; Kumar et al., 2010; Zhu et al., 2018). Thus, in PDPN where chronic painful conditions of specifically lower limbs causes reduced sensory thresholds, mobility, depression and impaired quality of life, neurodynamic mobilization can play a crucial role in addressing the same (Boyd et al., 2017). Changes in excursion of peripheral nerves were also seen in dynamic ultrasonography while treating Diabetic neuropathy patients with neurodynamic mobilization (Coppieters et al., 2015).

1.5 Effects of Diabetes and role of foot exercises in PDPN

Patients with PDPN has comparatively higher prevalence to develop comorbidities and are at high risk for foot ulcers and amputations (Ritzwoller et al., 2009). Another complication of long-term hyperglycaemia is altered biomechanics of foot that develops due to abnormally high plantar pressures and altered gait resulting from reduced range of motion and muscle weakness (Francia et al., 2015; Hajrasouliha et al., 2005). Peripheral neuropathy associated with diabetes is also known to decline functions of skeletal muscles caused by reduce muscle mass, impaired muscular contraction and muscle wasting (Parasoglou et al., 2017). Muscle atrophy is also linked with increased inflammatory mediators like TNF-alpha and interleukin-6 (Visser et al., 2002), seen in

PDPN. Though, physical exercises are known to improve muscle mass, strength, glucose control, cardiorespiratory fitness, still majority of diabetic population are unable to exercise regularly due to musculoskeletal pains caused by the same (Cox et al., 2020). Addition of simple non weight bearing foot exercises can be beneficial in restoring muscular flexibility and mobility of foot and ankle joint (Win et al., 2020). Stretching and strengthening exercises of foot are also known to improve foot biomechanics in diabetic population (Sartor et al., 2012).

Clinical management of PDPN is difficult, though many pharmacological agents like anti-depressants and anti-convulsant, tramadol, opioids, topical capsaicin and tapentadol are available but relief in pain is limited and is associated with various side effects (Rosenstock et al., 2004; Staudt et al., 2020). Neuromodulation therapies that are proven to be clinically effective and statistically significant in relieving neuropathic pain in PDPN are TENS (Gossrau et al., 2011; Kumar et al., 1998; Metka et al., 2009; Naderi Nabi et al., 2015; Shahanawaz, 2014),Electrical stimulation (Thakral et al., 2013), Frequency-modulated electromagnetic neural stimulation (FREMS) (Bosi et al., 2013), Laser (Shashi Kumar et al., 2015; Zinman et al., 2004) and spinal cord stimulation (Galan et al., 2020; Jin et al., 2010; Petersen et al., 2021). Effects of yoga (Baute et al., 2019a), aerobic exercises (Yoo et al., 2015) and whole body vibration (Kessler,2013) in managing PDPN are also well established in literature.

Literature also suggests few studies investigating the effect of Neurodynamic mobilization on Diabetic Peripheral neuropathy, (Singh et al .,2012 ; Doshi & Singarvelan, 2019) and in neuropathic pains associated with diabetes mellitus (Kumar et al., 2010). Howsoever such studies have used limited outcome measures and seen effects of tibial nerve mobilization only. Few studies are also available proving the effect of Neurodynamic mobilization in PDPN in animal models (Zhu et al., 2018) and role of Neurodynamic mobilization in neuropathic pain and dysfunction in cadavers (Gilbert et al., 2014, 2015).

With best of our acquaintance there is a scarcity of research investigating the effect of Neurodynamic mobilization of tibial, sural as well as peroneal nerve in patients of PDPN. Purpose of this study is to observe combined effects of Neurodynamic mobilization of tibial, sural, and peroneal nerve along with Foot exercises as treatment and to compare the efficacy of this treatment protocol with experimental group B that will receive (TENS and Foot exercises) and control group which will receive Foot exercises alone in patients with PDPN.

2. Review of Literature

2.1 Literature review on role of TENS in DPN/ PDPN

(Kumar et al., 1998): The authors compared the effects TENS with sham therapy in 26 patients in age group of 31-70 years, diagnosed with PDPN and symptomatic from more than 2 months. This was a study of 20 weeks in which all patients who failed to have pain relief by amitriptyline were randomised into TENS and Sham group. Current perception test was done using a neurometer and painful symptoms using Analog scale and grading system. TENS parameters used were 35 mA, 35volts, 2-70 Hz. The study concluded that TENS given over a period of 12 weeks was effective in improving outcome measures in patients who failed to improve with amitryptiline.

(Forst et al., 2004): In this study authors compared effects of TENS (4 Hz/280 ms; 5–70 mA) 30 minutes daily with placebo in 19 patients of PDPN for 12 weeks. Changes in VAS, new total symptom score, sensory nerve thresholds and microvascular functions were measured at the beginning of study, at 4 weeks and at 12 weeks. Significant improvements were noticed in all outcome measures in TENS group.

(Metka et al., 2009): A Randomised clinical trial with 69 patients of PDPN was screened using MNSI and Quantitative sensory testing having neuropathic pain in lower limbs from atleast 6 months. The study compared effects of TENS (100 Hz,0.2 ms) with pregabalin (2 × 75 mg/day) in first week, 2 × 150 mg/day for two weeks, later reduced to 2 × 75 mg/day for one week, then withdrawn and with combined effects of Pregabalin and TENS for a period of 3 weeks. Pain was assessed using 100 mm VAS scale and quality of life using SF-36 questionnaire. According to the results of study, TENS was considered equally effective as other two groups and can prove to be an effective addition or an alternative to analgesics in treatment of PDPN.

(Gossrau et al., 2011): In this study authors compared Microburst TENS (2 HZ,30-40 mA) with Placebo group on 41 patients of PDPN. TENS was given for 30 minutes, 3 times in a week. Outcome measures included NPS and Pain disability index. Authors concluded TENS was no superior to placebo group.

(Bulut et al., 2011): In this study 40 patients with PDPN were divided randomly into TENS group and Placebo group. Patients in TENS group were given TENS at 80 HZ and amplitude that can cause paraesthesia, for 30 minutes daily for 20 days at Lumbar spine. VAS and Pain grades were

compared at baseline, 5th day, 10th day and 20th day. Significant improvements were noticed in both outcome measures after 20 days of treatment in TENS group.

(Shahanawaz, 2014): In this Randomised controlled trial author compared high TENS (100hz, 200-400 msec) with placebo in 30 patients with PDPN in age group of 40-70 years. Patients were given 6 sessions per week twice daily of TENS for 20 minutes for a period of 4 weeks. The study concluded that Experimental group that received TENS were significantly improved as per Visual analogous scale.

(Naderi Nabi et al., 2015): In this study authors compared the effects of TENS with Pulsed radiofrequency lumbar sympathectomy in 60 patients of both genders having PDPN. Patients who did not have relief with conservative treatment from at least 6 months, with Hba1c of less than 8% and had rating of 4 on NRC scale were included in the study. TENS was given at 80 Hz,50 amp.,0.2ms square pulse for 20 minutes for a period of 3 months (10sessions every other day). Pain and other symptoms were measured using NRS (Numerical rating scale). The study reported that both interventions showed significant improvements in rating of NRC.

(Serry et al., 2016): In present study, authors divided 60 patients having PDPN into 3 groups. Group A received TENS (15 HZ,250ms pulse width) 3 times a week, Group B received aerobic exercises (5 minutes warm up, 40 minutes aerobic exercises and 5 minutes cool down period), Group C received only pharmacological management. Pain as per VAS and medial plantar nerve conduction velocity was measured and compared pre and post treatment in all three groups. Authors concluded that Group A that received TENS was clinically and statistically better in pain parameters compared to exercise group and group receiving medicines, but no improvement was seen in nerve conduction velocity in any of group over a period of 8 weeks.

2.2 Literature review on effects of exercises on DPN/PDPN

(Kluding et al., 2012): In this pretest-posttest study authors compared the effects of strengthening and aerobic exercises before and after 10 weeks of treatment in patients with Diabetic peripheral neuropathy. Outcome measures used were VAS pain scale, MNSI questionnaire for investigating symptoms of neuropathy, functions of nerve and IENF branching and density. Authors concluded significant improvements in all outcome measures after 10 weeks of treatment.

(Kessler & Hong, 2013): In this study authors analysed effects of vibration in whole body in 12 patients with PDPN. 3-minute bout of WBV was given 3 days a week with frequency of 25 hz and 5mm amplitude. There were significant improvements in Pain as per neuropathic pain scale after every session and after 4 weeks of treatment.

(Yoo et al., 2015): In this Pilot study authors look out for effects of 16 weeks supervised aerobic exercise program on 14 patients with PDPN. Outcome measures were pain intensity and Pain interference with daily life. Secondary outcome measures were Vo2 max and Hb1ac, BMI and blood pressure. Authors achieved significant improvements in Pain perception and pain interference with daily activities in sleep and social participation after 16 weeks of intervention, though no improvements were noticed in Pain intensity and secondary outcome measures.

(Baute et al., 2019a): In this study authors have reviewed many studies looking for effect of Alternative and complementary medicine in Painful neuropathies. Authors concluded lifestyle modification, yoga, vitamin supplements and other exercises have caused improvement in Painful peripheral neuropathies caused due to many reasons mainly due to diabetes.

2.3 Literature review on effects of Neurodynamic mobilization on Neuropathic pains

(George, 2002): This is a case series of six patients having pain in lower back, between age of 38 to 51 years. These patients were treated by slump stretching techniques (neural mobilization in slump position and neural mobilization in modified SLR) after a warmup session of stretching and stationary cycling, change in location of symptoms, Improvement in symptoms and centralization of symptoms were measured using a body chart and intensity by using a 0-10 scale. Author concluded the aforesaid intervention resulted in reduced pain intensity and proximal localization of pain and other symptoms.

(Cleary, 2006): In this clinical review author discussed and summarized various conservative methods of treatment for Radial tunnel syndrome available so far in literature. He concluded the use of ultrasonic therapy, Radial nerve gliding exercises, ergonomic training and functional strengthening exercises for scapular muscles and rotator cuff muscles are most considered interventions for clinical and statistically significant improvements in managing symptoms and dysfunctions associated with radial tunnel syndrome.

(Bialosky et al., 2009): In this study 40 female subjects (18-70 years of age) of Carpal tunnel syndrome were divided randomly into neurodynamic mobilization group and sham group. Patients in intervention group received neurodynamic mobilization of median nerve with neck bending to opposite side. During first three sessions 5 sets of 10 cycles were given and sets were increased to 7 in next three sessions. Patients in sham group also received neurodynamic mobilization with reduced anatomical stress in median nerve and with neutral spine. Treatment was given 2 times per week for 3 weeks. Authors noticed significant improvements in both groups in pain intensity, upper limb dysfunctions, mechanical and pressure pain threshold. Temporal summation was reduced only in patients receiving neurodynamic mobilization. Outcome measures used were Neuropathic rating scale, DASH questionnaire, Grip strength, and Monofilament test and nerve conduction studies.

(Oskay et al., 2010): In this study authors evaluated 17 patients in age group of 35-50 years with cubital tunnel syndrome, having grade 1 or 2 neuropathy and symptomatic from at least 5 weeks. Treatment protocol included pulsed ultrasonic therapy (1 watt/cm square) for 5 minutes and Neurodynamic mobilization (Sliding techniques) of ulnar nerve was given. Patients were also asked to do some neurodynamic exercises 10 times daily as home programme. The protocol was followed for 8 weeks and 3 sessions were given per week. In second week, patients were also given progressive strengthening exercises using dumbbells, therabands and closed chain exercises using swiss ball. Authors concluded that above combination brought significant improvements in Pain, Tinel sign, upper limb Disability, grip strength and pinch strength as per VAS-P, VAS-T, DASH scale, dynamometer and pinch meter respectively. Improvements in sensations and functionality were also noticed after 8 weeks to 12 weeks in follow up.

(Sharma & Sheth, 2017): In this study authors compared combination of neurodynamic mobilization and conventional physical therapy with conventional physical therapy (hot packs, core stabilization, isometric back exercises) alone in patients with lumbosacral radiculopathy. Total of six sessions were given for six days per week. Patients between ages of 25-50 were considered. Outcome measures used were Numeric pain rating scale and modified oswestry disability index. Authors concluded that group receiving combination of Neurodynamic mobilization and conventional physical therapy showed more significant improvements in pain and improved functions than conventional physiotherapy.

(Talebi et al., 2018): In this study 30 Diabetic Patients with CTS were divided into TENS group and Manual therapy group randomly. Patients in conventional group (TENS and ultrasound) was given TENS at 80HZ, 60microsec.for 20 minutes. Ultrasonic therapy was given at 1 MHz, 1 watt per cm square intensity 5 min on carpal tunnel. Patients in manual therapy group received Neurodynamic mobilization and manual release technique of median nerve for 25 minutes. Both groups received treatment for 4 weeks. Total of 3 sessions were given per week. Manual therapy group showed significant improvements in all outcome measures whereas modality group received improvements in VAS and symptom severity scale.

2.4 Literature Review on effects of Neurodynamic mobilization on Fluid dynamics

(Gilbert et al., 2014): In this pretest-posttest study design six matched pairs of excised sections of sciatic nerve were taken from cadavers of both gender and dye mixture of human plasma and toluidine blue stock solution was injected into proximal third of the sciatic nerve under the epineurium. To produce a response similar to neural mobilization a material tester was used so that repetitive stretch/ relax cycles were given to the nerve segment. 5-stretch/relax cycles per minute were given. Dye spread measurement was taken after 25 mobilization cycles. Increased fluid movement was noted in experimental segments and not in control segments in which readings were taken after 5 minutes of rest of dye injection.

(Gilbert et al., 2015): This study was performed to assess the effect of neural mobilization on fluid dynamics in unembaled cadavers. Seven cadavers of both gender were taken and a dye was injected using digital calipers in fourth lumbar nerve root deep to epineurium. After initial measurements of proximal and distal dye spread was taken, it's allowed to stabilize for around 15 minutes. Neurodynamic mobilization was performed in experimental limb and post measurements of longitudinal spread of dye were taken. No mobilization was performed on control limb and measurement was taken after 5 minutes of spread of dye. Results of the study indicated dispersion of intraneural fluid post mobilization within the neural tissue of L4 nerve root. This study suggested that neural tissue mobilization aims to preserve neural function by reducing intraneural oedema.

2.5 Literature review on effects of Neurodynamic mobilization in DPN

(Kumar et al,. 2010): In this study authors included 32 patients with neuropathic pain in Diabetes mellitus by convenient sampling and randomly divided them in control group and experimental group. Control group received analgesics, glycaemic control medication, lifestyle modification and walking. Experimental group received tibial nerve mobilization (Sliders and tensioners) and nerve massage in addition to control group for five weeks. Outcome measures used were vibration perception thresholds, neuropathic pain severity, neuropathy specific quality of life (NeuroQoL) and SLR range of motion. Experimental group received Active movements of knee, ankle and foot, Passive stretching for plantar fascia, gastrosoleus, hamstrings and rectus femoris muscles, Nerve massage and Tibial nerve mobilization (Slider/tensioner techniques, 5 repetition for 3 minutes). Both groups achieved significant improvements, however the experimental group achieved more significant improvements in all outcome measures.

(Singh et al., 2012): In this study authors included 30 male patients in age group of 40 to 65 years with DPN having vibration perception threshold less ≤ 25. Patients were divided randomly into control group and experimental group. Experimental group received tibial nerve mobilization for 10 minutes. Each mobilization was given for 30 seconds with one minute rest between each glide. After 21 days of treatment significant improvement was noticed in Vibration perception threshold values.

(Boyd et al., 2017): In this quasi-experimental study 20 patients above 18 years, diagnosed with Diabetic peripheral neuropathy performed five neurodynamic exercises on their right leg for 10 minutes. SLR was measured before and after exercises using handheld digital inclinometer. Modified Back Questionnaire, MNSI, MDNS, VPT were used to measure degree of neuropathy. Each exercise was performed for 30 s with rest of 60 s between each exercise. Authors concluded increased range of motion of SLR after the session in all participants. There were no adverse effects or provocation of symptoms following these exercises in any of study participants.

(Doshi & Singarvelan, 2019): In this Pretest-posttest study authors included 20 patients of diabetic neuropathy in age group of 50 to 60 years. Intervention given to all patients was tibial nerve mobilization for 3 weeks. Total 5 sessions were given every week. NCV of sural nerve was

compared before and after 3 weeks of treatment. Significant improvement was noticed in NCV as well as Pain and other symptoms of DPN.

2.6 Literature review on effect of Neurodynamic mobilization in PDPN

(Zhu et al., 2018): In this study, authors compared three groups of rats with n=6 in each group. All the rats were given injection of STZ to induce diabetes. Once diabetes was confirmed after three days, rats underwent a behavior test of 7 days to confirm PDN. All the rats were then randomly divided into control group (Diabetic rats), PDN group and PDN neural mobilization group. All group received behavior test daily, but the neural mobilization group received neurodynamic mobilization of right sciatic nerve after giving them anesthesia with 3% isoflurane gas. Neural mobilization was given by oscillating ankle in dorsi/plantar flexion pattern. This group rats were given behavior test after they recovered from anesthesia. 5 sessions of mobilization were given every week for three weeks. Mechanical pain sensitivity was measured using von frey monofilament test. Findings reveal that rats develop severe mechanical hypersensitivity after diabetes was induced. Data was collected on day 7, 14, 21 and 28 th day after STZ injection. Mechanical allodynia was significantly reduced in group receiving neurodynamic mobilization. Concentration of pro inflammatory mediators (Interleukin -1beta, TNF-alpha) was also lowered significantly in sciatic nerve branches and trunk in neural mobilization group.

2.7 Literature review on effects of Neurodynamic mobilization on nerve excursion

(Coppieters et al., 2015): In this study 15 healthy and asymptomatic subjects of both genders were taken. These subjects underwent six different sliding and tensioner neurodynamic exercises for sciatic nerve. A high-resolution ultrasound recorded the sciatic nerve longitudinal movements while performing the aforesaid exercises. Electro goniometer was used to verify angles at hip and knee joints. This study concluded that different excursion of sciatic nerve is observed in different movements. Thus, indicating different biomechanical effects produced by different neurodynamic exercises can be utilized clinically in different dysfunctions.

2.8 Literature review on effects of Foot exercises on PDPN/DPN

(Sartor et al., 2014): In this study 55 patients in age group of 45 to 65 years with Diabetic polyneuropathy were divided randomly into two groups group. Usual care and medicines for glucose control were given to control group, while the experimental group received foot/ankle exercises and gait training. Exercises were given for 40 to 60 minutes, two times a week for 12

weeks. Assessment was done at baseline, end of 12 week and follow up at 24 weeks. Outcome measure used were gait changes, peak pressure, pressure in six foot-areas, velocity of centre of pressure, functions of intrinsic and extrinsic muscles, tests to analyse functions of foot and ankle. Authors concluded that inclusion of strengthening exercises of foot and ankle musculature and range of motion exercises of foot resulted in proper distribution of plantar pressure, change in foot roll over during gait and enhanced functions of foot. Significant improvements were also noticed in MNSI scores of experimental group after 12 weeks.

(Parasoglou et al., 2017): In this review authors discussed the effect of DPN on skeletal muscles and elaborates the role of exercises for the same. According to the author long term diabetic neuropathy results in muscle atrophy, loss of muscle power and strength. Consequently, leading to impaired balance, gait, increased plantar pressure and amputations. Many studies were discussed in this review that shows effectiveness of foot exercises.

(Win et al., 2020) : This is an 8-week study in which author compared two groups of diabetic neuropathy patients post treatment and at 16 week follow up. Control group received usual care and education regarding diabetic foot, whereas experimental group received hand, finger and foot exercises. Outcome measures used in study were Patient Neurotoxicity Questionnaire to assess activities of daily living, monofilament and vibration test were used to assess severity of neuropathy. Pain was assessed using behavioral rating scale and Visual Analog Scale. Hand functions were assessed using grip test, pinch test and finger counting time, while foot functions were assessed using Timed Up and Go tests. Authors concluded that significant improvements were noticed in exercise group as measured with all outcome measures in pain, neuropathy severity, activities of daily living and functions of hand and foot.

3. Description of Broad area

3.1 Neurodynamic exercises and its role in Painful Diabetic peripheral neuropathy

Painful Diabetic peripheral neuropathy is characterized by debilitating pains that disturbs sleep and restricts mobility which interferes with activities of daily living and reduces social participation. As no single management strategy provides satisfactory pain relief patients often feel depressed and develops anxiety.

This study proposes to use a combination of neurodynamic mobilization and foot exercises in patients with PDPN to ensure a complete rehabilitation that works on neuropathic pain as well as associated motor dysfunctions to avoid long term complications.

3.2 Research gaps

1) Though role of neurodynamic mobilization in neuropathic pain is well established in literature, there is dearth of studies regarding role of neurodynamic mobilization in PDPN.

2) There is availability of literature on role of neurodynamic mobilization in PDPN in animal models and cadaver studies but lack of evidence regarding its role in human models.

3) Studies available so far on Painful diabetic peripheral neuropathy with neurodynamic mobilization as intervention do not provide very high level of evidence.

4) Few studies that have seen the effects of neurodynamic mobilization in PDPN have seen its effects only on tibial nerve, this study propose to see the effects on tibial, sural and peroneal nerves.

5) With best of our knowledge no study has been conducted to evaluate the effect of neural mobilization on sensory or motor nerve conduction studies in patients with PDPN.

3.3 Problem Statement

Treatments available so far for Painful Diabetic Peripheral neuropathy do not provide complete and satisfactory relief and thus results in further complications that leads to depression and impaired quality of life. There is need for more effective, less time consuming, easy to administer therapy with no side effects.

There is dearth of Randomised controlled trials proving the effectiveness of neurodynamic mobilization in Painful Diabetic Peripheral neuropathy. Combination of Neurodynamic mobilization and foot exercises can prove to be a promising management in such debilitating pains.

3.4 Research Question

1.Whether there is any effect of neurodynamic mobilization and foot exercises on Nerve conduction velocity in patients with PDPN?

2.Whether there is any effect of neurodynamic mobilization and foot exercises on pain, sensory symptoms and functions in patients with PDPN?

3.Whether there is any effect of neurodynamic mobilization and foot exercises on quality of life in patients with PDPN?

4.Whether there is any effect of neurodynamic mobilization and foot exercises on psychological status in Patients with PDPN?

5.Whether the combination of neurodynamic mobilization and foot exercises is more effective than TENS and Foot exercises and control group as per aforesaid outcome measures in patients PDPN?

4. Objectives of study

1. To measure changes in sensory and motor nerve conduction velocity of tibial nerve and peroneal nerve and sensory nerve conduction velocity of sural nerve after neurodynamic mobilization and foot exercises in patients with PDPN.

2. To measure changes in Pain, sensory symptoms and functions after neurodynamic mobilization and foot exercises in patients with PDPN.

3. To measure changes in Quality of life after neurodynamic mobilization and foot exercises in patients with PDPN.

4. To measure changes in psychological status after neurodynamic mobilization and foot exercises in patients with PDPN.

5. To compare the changes in above mentioned parameters brought about by neurodynamic mobilization and foot exercises with experimental group B that will receive TENS and Foot exercises and control group receiving foot exercises and education only in patients with PDPN.

5. Methodology

5.1 Sample

Patients with PDPN will be recruited from Sarvodaya hospital and research centre, sector 8 Faridabad, and other diabetic centres in Faridabad.

5.2 Sample Size

The number of patients were determined using software G-power 3.1.9.4 using the data changes in neuropathic pain score from study done by (Gossrau, etal.,2011) in which effect of TENS therapy was evaluated in PDPN. 32 subjects per group (including 15% dropout) was shown to be necessary based on effect size of 0. 494, alpha level 0.05 and power of 0.8. Hence the total sample size came out to be 96.

5.3 Study design

The study design will be Randomized controlled trial with three parallel groups (two experimental and one control group) with single blinding (Blinding of outcome assessor).

The subjects will be randomly allocated to the experimental and control group using block randomization with block size of three and allocation ratio of 1:1:1. The concealment of allocation will be ensured by using sequentially numbered, sealed and opaque envelopes. The study will be registered at CRTI (Clinical trial registry of India).

The ethical approval will be taken from Manav Rachna International Institute of Research and Studies. The research procedure will be conducted in accordance with the declaration of Helsinki, 1964.

5.4 Inclusion Criteria

1. Age between 50 and 70 years.
2. Diagnosed Diabetes Mellitus with at least 7 years of duration treated by diet, oral hypoglycaemics or insulin therapy.
3. BMI (Body mass index) between 18 and 29.9 kg/m^2 .
4. NDS (Neuropathy Disability score) more than 3.
5. Distal symmetrical or asymmetrical polyneuropathy with pain in the lower extremity for ≥6 months.
6. LANSS score (Leeds assessment of neuropathic symptoms and signs) ≥12.
7. Patients who can stand on both of their feet independently or using walking aids.

5.5 Exclusion Criteria

1. History or evidence of neurological disorders other than peripheral neuropathy associated with Diabetes mellitus.
2. Evidence of musculoskeletal dysfunctions like scoliosis, lumbar disc prolapse and lumbar spine associated radiculopathy.
3. History of any low back surgeries and lower limb surgeries.
4. History or evidence of plantar/foot ulcers.
5. History of Diabetic complications like severe nephropathy, severe retinopathy, severe hepatic disorders and significant cardiovascular impairment.
6. Receiving any other physiotherapy treatment for lower limb pain and other symptoms.

5.6 Variables

A. Dependent Variables

1. Nerve conduction studies
2. Quantitative sensory Testing
3. Ankle Proprioception
4. Pain
5. Quality of Life
6. Psychological Status
7. Neuropathy Disability Score

B. Independent Variables

1. TENS
2. Neurodynamic mobilization
3. Foot exercises and Patient Education

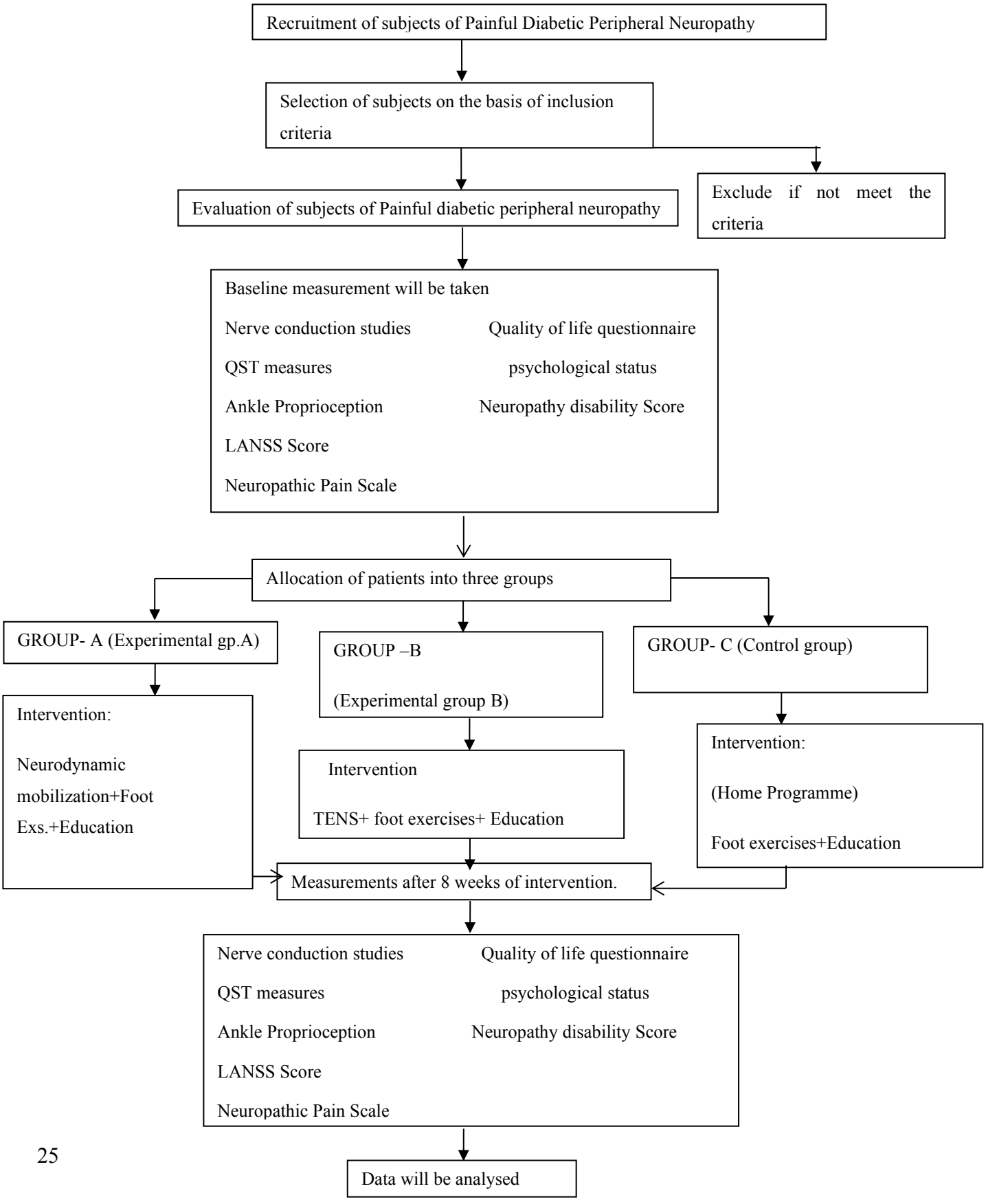
5.7 Procedure

Patients of PDPN will be recruited from Sarvodaya hospital and research centre sector 8, Faridabad and other diabetic clinics nearby, based on inclusion and exclusion criteria. Randomisation and enrolment of patients will be done. Assignment of patients will be done by investigator who will neither be part of assessment or interventions. All the information regarding the purpose and methodology of study will be given to patients. Each patient will be given their written consent in English/Hindi. They will be explained about their rights as study participants and all their information will be kept confidential.

5.8 Protocol

After obtaining demographic details and medical screening of patients a detailed physical examination of each patient will be conducted. Baseline measurements will include body composition, metabolic profile and outcome measures including Nerve conduction studies, Quantitative sensory testing, Ankle Proprioception, LANSS measurements, Neuropathic Pain Scale, Quality of life questionnaire, psychological status and Neuropathy Disability Score. They will be allocated into one of three groups as per randomization. Neurodynamic mobilization, foot exercises, education regarding glycaemic control and foot care will be given to group A. TENS, Foot exercises and education will be given to group B. Foot exercises and education will be given

to group C (Control group). Outcome measures will be taken at beginning of research work and after 8 weeks.



5.9 Interventions

1. Neurodynamic Mobilization

Slider and tensioner mobilization will be given for tibial nerve, peroneal nerve and sural nerve for symptomatic lower limbs as mentioned by shacklock (Shacklock, 2005).

Neurodynamic mobilization will be done by the physiotherapist specialized in manual therapy for 3 times/week for 8 weeks. Total 4 sets of 10 cycles of neurodynamic mobilization will be given daily with rest period of 1 min in each set.

2. Foot Exercises

Foot exercises will include foot taping, V shape making, Ankle rotation, tennis ball rolling. All the exercises will be repeated 5 to 10 times (as tolerated) on both feet one by one (Win et al., 2020). Foot Somatosensory Exercise: Patient will be asked to roll a small ball under feet.

3. TENS

TENS will be given 3 days a week for 8 weeks, 20 minutes daily with following parameters. (80 Hz, 2 to 3 times sensory threshold) (Naderi Nabi et al., 2015).

4. Patient Education

Patient education regarding glycaemic control and foot care will be provided to patients of all the groups. This will include general guidelines on monitoring and regulation of glucose levels, dietary counselling, regular self-examination and care of foot (Baute et al., 2019b; Clark et al., 2001; Iunes et al., 2014). Education will be provided after every two weeks by subject specialist. Duration of education class will be 20 minutes and it will be given to all patients in group of 5. A detailed pamphlet of guidelines will also be provided to all patients.

5.10 Outcome Measures

Primary Outcome Measures:

1. Nerve conduction studies

Nerve conduction studies will be done for tibial, peroneal and sural nerves bilaterally by qualified technician. NCS are considered as most reliable, accurate and sensitive test for detection of peripheral neuropathy (Nasseri et al., 1998).

2. **Quantitative Sensory testing:**

QST is a non-invasive method to quantify sensory functions. It includes mechanical threshold, Vibration perception threshold, thermal threshold and pressure pain threshold. It is considered as reliable method to assess sensory functions of large and small nerves (Siao & Cros, 2003).

a. **Mechanical threshold:** Von Frey monofilaments (10 grams) will be used to check mechanical threshold. First the patient will be explained the procedure by placing the filament on palm. Later we will stroke monofilament and press till it gets bend at different sites on bottom of foot and patient will be asked to communicate every time they feel it. An average of all readings will be taken once patient will not be able to appreciate exact location for 2 to 3 times (Baraz et al., 2014).

b. **Vibration perception threshold:** VPT will be measured using NEUROTOUCH device which is a multimodal and new device for screening peripheral neuropathy in Diabetes. The probe will be applied on foot of patient and reading of vibration perception threshold will be noted. It has specificity of 95 % and sensitivity of 80.7%. It has been found reliable and valid device in comparison to predicate devices. (Dasgupta et al., 2022; Maiya et al., 2020; Sharma & Maruthy, 2019).

c. **Thermal threshold detection:** This will be assessed using NEUROTOUCH device which is used to check warm and cold thermal sensory thresholds. In this transducer probe will be applied on sole of foot in randomly selected different foot areas. Patient will be asked to tell the examiner about when he will first feel the sensation of hot/cold. Average of three readings will be taken as thermal threshold of that patient. This has been used in various researches and is considered valid and reliable method for analysis of thermal perception threshold (Dasgupta et al., 2022; Maiya et al., 2020; (Sharma & Maruthy, 2019)

d. **Pressure pain threshold:** Pressure algometer of probe 1 cm square will be used to assess pressure pain threshold. Its value is recorded at the point of the first perception of Pain by patient. Reliability and validity of pressure algometer is well established (KInser et al., 2009).

3. **Ankle proprioception**

Ankle proprioception will be measured using digital or bubble inclinometer. Patients will be asked to maintain the targeted angle for dorsiflexion/plantar flexion and hold for 5 seconds. Then he will be asked to return to starting position and re attain the earlier angle without looking. Deviation in set angle will be recorded. (Ha et al., 2018; Willems et al., 2002)

4. **Pain and other symptoms of Painful diabetic peripheral neuropathy**

Leeds assessment of neuropathic symptoms and signs scale (LANSS) and Neuropathic Pain Scale (NPS) will be used to discriminate and quantify the intensity of neuropathic pain respectively.

a. **LANSS Scale**: Leeds assessment of neuropathic symptoms and signs scale will be used to distinguish neuropathic pain from nociceptive pain. This scale assesses type of pain and includes sensory testing for allodynia and altered pin prick threshold. It has maximum score of 24. If the pain score will be 12 or more, it is most likely considered as neuropathic pain. The reliability and validity of LANSS scale is well established (Bennett, 2001).
b. **Neuropathic Pain scale:** It measures the intensity of different kind of pain sensations experienced by patients of PDPN on a scale from 0 to 10, where 0 represents no pain and worst pain at 10. It is a valid and reliable tool to measure pain intensity (Galer & Jensen, 1997).

Secondary Outcome Measures:

1. **Quality of life:** Quality of life will be measured by Neuropathy specific Quality of life Questionnaire. This is a reliable and valid questionnaire (Smith et al., 2012) that measures physical and emotional aspect related to quality of life of PDPN patient. It includes six sub scales with total of 27 questions. It is a 5 point scale where 1 represents “never” and 5 represents “all the time” (Alam et al., 2017; Vileikyte et al., 2006).

2. **Psychological status:**

Psychological assessment will be done by using Pain catastrophising scale and Pain Self efficacy questionnaire.

a. Pain catastrophising scale: It is a 13-item scale designed to assess the feelings associated with feelings of helplessness, rumination and magnification caused by pain. It is a 5-point scale where higher value denotes higher intensity of pain (Pedler, 2010).

b. Pain self-efficacy questionnaire: It is a 10-item questionnaire used to assess how well patients are coping with pain without medications in performing different functional activities. It is a 6-point scale ranging from not at all confident at 0 to completely confident at 6 (Nicholas, 2007).

3. **NDS score**: Neuropathy Disability score examines severity of neuropathy by checking for appropriate or reduced sensations of vibration perception threshold, perceived sensations of pin prick and perception of temperature threshold on foot. It also examines presence, reinforced or absence of achilles reflex bilaterally. NDS score of more than 3 indicates neuropathy. It is considered as reliable and valid instrument to assess diabetic neuropathy (Höliner et al., 2013; Young et al., 1993).

6. Expected outcome of the study

Experimental Hypothesis:

1. There will be significant improvements in electrophysiological parameters of tibial, peroneal and sural nerve after neurodynamic mobilization in patients with PDPN.
2. There will be significant improvements in pain, sensory symptoms and functions after neurodynamic mobilization in patients with PDPN.
3. There will be significant improvements in Quality of life and psychological status after neurodynamic mobilization in patients with PDPN.

Null hypothesis:

1. There will be no significant difference in electrophysiological parameters of the patients who will receive neurodynamic mobilization in comparison to patients in experimental group B and control group.
2. There will be no significant difference in Pain, Sensory symptoms and functions of patients who will receive neurodynamic mobilization in comparison to patients in other two groups.

3. There will be no significant difference in Quality of life and psychological status of patients who will receive neurodynamic mobilization in comparison to patients in other two groups.

7. References

Abbott, C. A., Malik, R. A., Van Ross, E. R. E., Kulkarni, J., & Boulton, A. J. M. (2011). Prevalence and characteristics of painful diabetic neuropathy in a large community-based diabetic population in the U.K. *Diabetes Care*, *34*(10), 2220–2224. https://doi.org/10.2337/dc11-1108

Ahmed, N. (2005). Advanced glycation endproducts - Role in pathology of diabetic complications. *Diabetes Research and Clinical Practice*, *67*(1), 3–21. https://doi.org/10.1016/j.diabres.2004.09.004

Alam, U., Fawwad, A., Shaheen, F., Tahir, B., Basit, A., & Malik, R. A. (2017). Improvement in Neuropathy Specific Quality of Life in Patients with Diabetes after Vitamin D Supplementation. *Journal of Diabetes Research*, *2017*. https://doi.org/10.1155/2017/7928083

Allen, M., Doherty, T., Rice, C., & Kimpinski, K. (2016). *Physiology in Medicine:neuromuscular consequencies of diabetic neuropathy*. 1–6. https://doi.org/doi:10.1152/japplphysiol.00733.2015.

Baraz, S., Zarea, K., Shahbazian, H. B., & Latifi, S. M. (2014). Comparison of the accuracy of monofilament testing at various points of feet in peripheral diabetic neuropathy screening. *Journal of Diabetes and Metabolic Disorders*, *13*(1), 1–7. https://doi.org/10.1186/2251-6581-13-19

Basson, A., Olivier, B., Ellis, R., Coppieters, M., Stewart, A., & Mudzi, W. (2017). The effectiveness of neural mobilization for neuromusculoskeletal conditions: A systematic review and meta-Analysis. *Journal of Orthopaedic and Sports Physical Therapy*, *47*(9), 593–615. https://doi.org/10.2519/jospt.2017.7117

Baute, V., Zelnik, D., Curtis, J., & Sadeghifar, F. (2019a). Complementary and Alternative Medicine for Painful Peripheral Neuropathy. In *Current Treatment Options in Neurology* (Vol. 21, Issue 9). https://doi.org/10.1007/s11940-019-0584-z

Baute, V., Zelnik, D., Curtis, J., & Sadeghifar, F. (2019b). Complementary and Alternative

Medicine for Painful Peripheral Neuropathy. *Current Treatment Options in Neurology*, *21*(9). https://doi.org/10.1007/s11940-019-0584-z

Bennett, M. (2001). The LANSS Pain Scale: The Leeds assessment of neuropathic symptoms and signs. *Pain*, *92*(1–2), 147–157. https://doi.org/10.1016/S0304-3959(00)00482-6

Bialosky, J. E., Bishop, M. D., Price, D. D., Robinson, M. E., Vincent, K. R., & George, S. Z. (2009). A randomized sham-controlled trial of a neurodynamic technique in the treatment of carpal tunnel syndrome. *Journal of Orthopaedic and Sports Physical Therapy*, *39*(10), 709–723. https://doi.org/10.2519/jospt.2009.3117

Blesneac, I., Themistocleous, A. C., Fratter, C., Conrad, L. J., Ramirez, J. D., Cox, J. J., Tesfaye, S., Shillo, P. R., Rice, A. S. C., Tucker, S. J., & Bennett, D. L. H. (2018). Rare NaV1.7 variants associated with painful diabetic peripheral neuropathy. In *Pain* (Vol. 159, Issue 3). https://doi.org/10.1097/j.pain.0000000000001116

Booya, F., Bandarian, F., Larijani, B., Pajouhi, M., Nooraei, M., & Lotfi, J. (2005). Potential risk factors for diabetic neuropathy: A case control study. *BMC Neurology*, *5*, 1–5. https://doi.org/10.1186/1471-2377-5-24

Bosi, E., Bax, G., Scionti, L., Spallone, V., Tesfaye, S., Valensi, P., & Ziegler, D. (2013). Frequency-modulated electromagnetic neural stimulation (FREMS) as a treatment for symptomatic diabetic neuropathy: Results from a double-blind, randomised, multicentre, long-term, placebo-controlled clinical trial. *Diabetologia*, *56*(3), 467–475. https://doi.org/10.1007/s00125-012-2795-7

Boyd, B. S., & Dilley, A. (2014). Altered tibial nerve biomechanics in patients with diabetes mellitus. *Muscle and Nerve*, *50*(2), 216–223. https://doi.org/10.1002/mus.24155

Boyd, B. S., Nee, R. J., & Smoot, B. (2017). Safety of lower extremity neurodynamic exercises in adults with diabetes mellitus: a feasibility study. *Journal of Manual and Manipulative Therapy*, *25*(1), 30–38. https://doi.org/10.1080/10669817.2016.1180772

Boyd, B. S., Wanek, L., Gray, A. T., & Topp, K. S. (2010). Mechanosensitivity during lower extremity neurodynamic testing is diminished in individuals with Type 2 Diabetes Mellitus

and peripheral neur1. Boyd BS, Wanek L, Gray AT, Topp KS. Mechanosensitivity during lower extremity neurodynamic testing is diminishe. *BMC Neurology*, *10*, 5–8.

Bulut, M., ÖZCAN, A., ÇAKAN, T., BEKTAŞ, M., & ÇULHA, C. (2011). The Comparison of Effectiveness of TENS and Placebo TENS in Peripheral Neuropathic Pain in Patients with Type II Diabetes Mellitus. *Turkiye Klinikleri Journal of Medical Sciences*, *31*(4), 913–918. https://doi.org/10.5336/medsci.2010-18141

Cade, W. T. (2008). Diabetes-related microvascular and macrovascular diseases in the physical therapy setting. *Physical Therapy*, *88*(11), 1322–1335. https://doi.org/10.2522/ptj.20080008

Callaghan, B. C., Cheng, H. T., Stables, C. L., Smith, A. L., & Feldman, E. L. (2012). Diabetic neuropathy: Clinical manifestations and current treatments. *The Lancet Neurology*, *11*(6), 521–534. https://doi.org/10.1016/S1474-4422(12)70065-0

Carta, G., Gambarotta, G., Fornasari, B. E., Muratori, L., El Soury, M., Geuna, S., Raimondo, S., & Fregnan, F. (2021). The neurodynamic treatment induces biological changes in sensory and motor neurons in vitro. *Scientific Reports*, *11*(1), 1–12. https://doi.org/10.1038/s41598-021-92682-2

Cauda, F., Sacco, K., D'Agata, F., Duca, S., Cocito, D., Geminiani, G., Migliorati, F., & Isoardo, G. (2009). Low-frequency BOLD fluctuations demonstrate altered thalamocortical connectivity in diabetic neuropathic pain. *BMC Neuroscience*, *10*, 1–14. https://doi.org/10.1186/1471-2202-10-138

Clark, charles M., FRADKIN, J. E., HISS, R. G., & LORENZ, R. A. (2001). Program , Changing the Way Diabetes. In *American Journal of Clinical Nutrition*.

Cleary, C. K. (2006). Management of Radial Tunnel Syndrome: A Therapist's Clinical Perspective. *Journal of Hand Therapy*, *19*(2), 186–191. https://doi.org/10.1197/j.jht.2006.02.020

Coppieters, M. W., Andersen, L. S., Johansen, R., Giskegjerde, P. K., Hivik, M., Vestre, S., & Nee, R. J. (2015). Excursion of the sciatic nerve during nerve mobilization exercises: An in vivo cross-sectional study using dynamic ultrasound imaging. *Journal of Orthopaedic and*

Sports Physical Therapy, *45*(10), 731–737. https://doi.org/10.2519/jospt.2015.5743

Cox, E. R., Gajanand, T., Burton, N. W., Coombes, J. S., & Coombes, B. K. (2020). Effect of different exercise training intensities on musculoskeletal and neuropathic pain in inactive individuals with type 2 diabetes – Preliminary randomised controlled trial. *Diabetes Research and Clinical Practice*, *164*, 108168. https://doi.org/10.1016/j.diabres.2020.108168

Da Silva, J. T., Dos Santos, F. M., Giardini, A. C., De Oliveira Martins, D., De Oliveira, M. E., Ciena, A. P., Gutierrez, V. P., Watanabe, I. S., De Britto, L. R. G., & Chacur, M. (2015). Neural mobilization promotes nerve regeneration by nerve growth factor and myelin protein zero increased after sciatic nerve injury. *Growth Factors*, *33*(1), 8–13. https://doi.org/10.3109/08977194.2014.953630

Dasgupta, R., Jebasingh, F., Thomas, N., KN, M., Sharma, S., & Saravanan, B. (2022). NEURO TOUCH: A novel digital device for assessment and screening of peripheral neuropathy. In *Foot* (Vol. 51). https://doi.org/10.1016/j.foot.2021.101888

Davies, M., Brophy, S., Williams, R., & Taylor, A. (2006). The prevalence, severity, and impact of painful diabetic peripheral neuropathy in type 2 diabetes. *Diabetes Care*, *29*(7), 1518–1522. https://doi.org/10.2337/dc05-2228

Domingues, M. (2018). Diabetic Peripheral Neuropathy and Neurodynamics. *International Physical Medicine & Rehabilitation Journal*, *3*(1), 3–5. https://doi.org/10.15406/ipmrj.2018.03.00075

Doshi, M. K., & Singarvelan, R. M. (2019). *Effect of Tibial Nerve Mobilization on Nerve Conduction Velocity in Diabetic Neuropathy Patient*. *9*(May), 218–224.

Efstathiou, M. A., Stefanakis, M., Savva, C., & Giakas, G. (2015). Effectiveness of neural mobilization inpatients with spinal radiculopathy: Acritical review. *Journal of Bodywork and Movement Therapies*, *19*(2), 205–212. https://doi.org/10.1016/j.jbmt.2014.08.006

Erbas, T., Ertas, M., Yucel, A., Keskinaslan, A., Senocak, M., Aktekin, B., Altunbas, H., Aydin, H., Balci, M. K., Karayalcin, U., Karsli, B., Yazicioglu, G., Yegin, A., Asik, I., Ates, Y., Cin, M. O., Gullu, S., Kesik, Y., Mutluer, N., … Zarifoglu, M. (2011). Prevalence of peripheral

neuropathy and painful peripheral neuropathy in Turkish diabetic patients. *Journal of Clinical Neurophysiology*, *28*(1), 51–55. https://doi.org/10.1097/WNP.0b013e3182051334

Feldman, E. L., Callaghan, B. C., Pop-Busui, R., Zochodne, D. W., Wright, D. E., Bennett, D. L., Bril, V., Russell, J. W., & Viswanathan, V. (2019). Diabetic neuropathy. *Nature Reviews Disease Primers*, *5*(1). https://doi.org/10.1038/s41572-019-0092-1

Forst, T., Nguyen, M., Forst, S., Disselhoff, B., Pohlmann, T., & Pfützner, A. (2004). Impact of low frequency transcutaneous electrical nerve stimulation on symptomatic diabetic neuropathy using the new Salutaris® device. In *Diabetes, Nutrition and Metabolism - Clinical and Experimental* (Vol. 17, Issue 3, pp. 163–168). http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L391172777

Francia, P., Anichini, R., De Bellis, A., Seghieri, G., Lazzeri, R., Paternostro, F., & Gulisano, M. (2015). Diabetic foot prevention: The role of exercise therapy in the treatment of limited joint mobility, muscle weakness and reduced gait speed. *Italian Journal of Anatomy and Embryology*, *120*(1), 21–32. https://doi.org/10.13128/IJAE-16470

Galan, V., Scowcroft, J., Chang, P., Li, S., Staats, P., Rotte, A., & Subbaroyan, J. (2020). 10-kHz spinal cord stimulation treatment for painful diabetic neuropathy: results from post-hoc analysis of the SENZA-PPN study . *Pain Management*, *10*(5), 291–300. https://doi.org/10.2217/pmt-2020-0033

Galer, B. S., Gianas, A., & Jensen, M. P. (2000). Painful diabetic polyneuropathy: Epidemiology, pain description, and quality of life. *Diabetes Research and Clinical Practice*, *47*(2), 123–128. https://doi.org/10.1016/S0168-8227(99)00112-6

Galer, B. S., & Jensen, M. P. (1997). Development and preliminary validation of a pain measure specific to neuropathic pain: The Neuropathic Pain Scale. *Neurology*, *48*(2), 332–338. https://doi.org/10.1212/WNL.48.2.332

George, S. Z. (2002). Characteristics of patients with lower extremity symptoms treated with slump stretching: A case series. *Journal of Orthopaedic and Sports Physical Therapy*, *32*(8), 391–398. https://doi.org/10.2519/jospt.2002.32.8.391

Gilbert, K. K., Smith, M. P., Sobczak, S., James, C. R., Sizer, P. S., & Brismée, J.-M. (2015). Effects of lower limb neurodynamic mobilization on intraneural fluid dispersion of the fourth lumbar nerve root: An unembalmed cadaveric investigation. *Journal of Manual and Manipulative Therapy*, *23*(5), 239–245. https://doi.org/10.1179/2042618615Y.0000000009

Gilbert, Roger James, C., Apte, G., Brown, C., Sizer, P. S., Brismeé, J. M., & Smith, M. P. (2014). Effects of simulated neural mobilization on fluid movement in cadaveric peripheral nerve sections: Implications for the treatment of neuropathic pain and dysfunction. *Journal of Manual and Manipulative Therapy*, *23*(4), 219–225. https://doi.org/10.1179/2042618614Y.0000000094

Gore, M., Brandenburg, N. A., Hoffman, D. L., Tai, K. S., & Stacey, B. (2006). Burden of Illness in Painful Diabetic Peripheral Neuropathy: The Patients' Perspectives. *Journal of Pain*, *7*(12), 892–900. https://doi.org/10.1016/j.jpain.2006.04.013

Gossrau, G., Wähner, M., Kuschke, M., Konrad, B., Reichmann, H., Wiedemann, B., & Sabatowski, R. (2011). Microcurrent Transcutaneous Electric Nerve Stimulation in Painful Diabetic Neuropathy: A Randomized Placebo-Controlled Study. *Pain Medicine 2011*, *12*(wiley periodicals), 953–960.

Ha, S. Y., Han, J. H., & Sung, Y. H. (2018). Effects of ankle strengthening exercise program on an unstable supporting surface on proprioception and balance in adults with functional ankle instability. *Journal of Exercise Rehabilitation*, *14*(2), 301–305. https://doi.org/10.12965/jer.1836082.041

Hajrasouliha, A. R., Tavakoli, S., Esteki, A., Nafisi, S., & Noorolahi-Moghaddam, H. (2005). Abnormal viscoelastic behaviour of passive ankle joint movement in diabetic patients: An early or a late complication? *Diabetologia*, *48*(6), 1225–1228. https://doi.org/10.1007/s00125-005-1757-8

Hernández-Secorún, M., Vidal-Peracho, C., Márquez-Gonzalvo, S., Corral-De-toro, J., Müller-Thyssen-uriarte, J., Rodríguez-Sanz, J., Lucha-López, M. O., Tricás-Moreno, J. M., & Hidalgo-García, C. (2021). Exercise and manual therapy for diabetic peripheral neuropathy: A systematic review. *Applied Sciences (Switzerland)*, *11*(12).

https://doi.org/10.3390/app11125665

Hoeijmakers, J. G. J., Faber, C. G., Merkies, I. S. J., & Waxman, S. G. (2015). Painful peripheral neuropathy and sodium channel mutations. *Neuroscience Letters*, *596*, 51–59. https://doi.org/10.1016/j.neulet.2014.12.056

Höliner, I., Haslinger, V., Lütschg, J., Müller, G., Barbarini, D. S., Fussenegger, J., Zanier, U., Saely, C. H., Drexel, H., & Simma, B. (2013). Validity of the neurological examination in diagnosing diabetic peripheral neuropathy. *Pediatric Neurology*, *49*(3), 171–177. https://doi.org/10.1016/j.pediatrneurol.2013.03.014

Huang, Q., Chen, Y., Gong, N., & Wang, Y. X. (2016). Methylglyoxal mediates streptozotocin-induced diabetic neuropathic pain via activation of the peripheral TRPA1 and Nav1.8 channels. *Metabolism: Clinical and Experimental*, *65*(4), 463–474. https://doi.org/10.1016/j.metabol.2015.12.002

IDF Diabetes Atlas. (2021). In *IDF Diabetes Atlas 10th edition,International Diabetes Federation*. https://diabetesatlas.org/

Iunes, D. H., Rocha, C. B. J., Borges, N. C. S., Marcon, C. O., Pereira, V. M., & Carvalho, L. C. (2014). Self-care associated with home exercises in patients with type 2 diabetes mellitus. *PLoS ONE*, *9*(12), 1–13. https://doi.org/10.1371/journal.pone.0114151

Jamal, A., Ahmad, I., Ahamed, N., Azharuddin, M., Alam, F., & Hussain, M. E. (2020). Whole body vibration showed beneficial effect on pain, balance measures and quality of life in painful diabetic peripheral neuropathy: a randomized controlled trial. *Journal of Diabetes and Metabolic Disorders*, *19*(1), 61–69. https://doi.org/10.1007/s40200-019-00476-1

Jambart, S., Ammache, Z., Haddad, F., Younes, A., Hassoun, A., Abdalla, K., Abou Selwan, C., Sunna, N., Wajsbrot, D., & Youseif, E. (2011). Prevalence of painful diabetic peripheral neuropathy among patients with diabetes mellitus in the Middle East region. *Journal of International Medical Research*, *39*(2), 366–377. https://doi.org/10.1177/147323001103900204

Jin, D. mei, Xu, Y., Geng, D. feng, & Yan, T. bin. (2010). Effect of transcutaneous electrical nerve

stimulation on symptomatic diabetic peripheral neuropathy: A meta-analysis of randomized controlled trials. *Diabetes Research and Clinical Practice*, *89*(1), 10–15. https://doi.org/10.1016/j.diabres.2010.03.021

Kessler, N. J., & Hong, J. (2013). Whole body vibration therapy for painful diabetic peripheral neuropathy: A pilot study. *Journal of Bodywork and Movement Therapies*, *17*(4), 518–522. https://doi.org/10.1016/j.jbmt.2013.03.001

KInser, A. M., Sands, W. A., & Stone, M. H. (2009). Reliability and validity of a pressure algometer. *Journal of Strength and Conditioning Research*, *23*(1), 2–4.

Kiyani, M., Yang, Z., Charalambous, L. T., Adil, S. M., Lee, H.-J., Yang, S., Pagadala, P., Parente, B., Spratt, S. E., & Lad, S. P. (2020). Painful diabetic peripheral neuropathy. *Neurology: Clinical Practice*, *10*(1), 47–57. https://doi.org/10.1212/cpj.0000000000000671

Kluding, P. M., Pasnoor, M., Singh, R., Jernigan, S., Farmer, K., Rucker, J., Sharma, N. K., & Wright, D. E. (2012). The effect of exercise on neuropathic symptoms, nerve function, and cutaneous innervation in people with diabetic peripheral neuropathy. *Journal of Diabetes and Its Complications*, *26*(5), 424–429. https://doi.org/10.1016/j.jdiacomp.2012.05.007

Kumar, Indeerjeet, S. J., Michael, S. A., & J.Marshall, H. (1998). *Diabetic Peripheral Neuro p a t h y E ffectiveness of electrotherapy and amitriptyline for symptomatic re l i e f*. *21*(8).

Kumar, P. S., Adhikari, P., & Jegananathan, P. (2010). *Immediate effects of longitudinal vs . Transverse tibial nerve massage on vibration perception thresholds and thermal perception thresholds in asymptomatic subjects : A pilot randomized clinical trial (UTRN 014427448-2101200878203)*. *3*(1), 13–23.

Kumar, P. S., Adhikari, P., & Prabhu, M. M. (2010). I ndian J ournal of Physiotherapy and Occupational Therapy. *Indian Journal of Physiotherapy and Occupational Therapy*, *4*(3).

Maiya, A. G., Parameshwar, A., Hande, M., & Nandalike, V. (2020). Relationship Between Glycated Hemoglobin and Vibration Perception Threshold in Diabetic Peripheral Neuropathy. *International Journal of Lower Extremity Wounds*, *19*(2), 120–124. https://doi.org/10.1177/1534734619882173

Metka, M., Marinček, Č., Vidmar, G., & Burger, H. (2009). Transcutaneous electrical nerve stimulation, pregabalin and their combination in patients with painful diabetic neuropathy: Effects on pain and quality of life. *Zdravniski Vestnik*, *78*(8), 371–379.

Naderi Nabi, B., Sedighinejad, A., Haghighi, M., Biazar, G., Hashemi, M., Haddadi, S., & Fathi, A. (2015). Comparison of transcutaneous electrical nerve stimulation and pulsed radiofrequency sympathectomy for treating painful diabetic neuropathy. *Anesthesiology and Pain Medicine*, *5*(5). https://doi.org/10.5812/aapm.29280

Nasseri, K., Strijers, R. L., Dekhuijzen, L. S., Buster, M., & Bertelsmann, F. W. (1998). Reproducibility of different methods for diagnosing and monitoring diabetic neuropathy. *Electromyography and Clinical Neurophysiology*, *38*(5), 295—299. http://europepmc.org/abstract/MED/9741007

Nee, R. J., & Butler, D. (2006). Management of peripheral neuropathic pain: Integrating neurobiology, neurodynamics, and clinical evidence. *Physical Therapy in Sport*, *7*(1), 36–49. https://doi.org/10.1016/j.ptsp.2005.10.002

Neto, T., Freitas, S. R., Marques, M., Gomes, L., Andrade, R., & Oliveira, R. (2017). Effects of lower body quadrant neural mobilization in healthy and low back pain populations: A systematic review and meta-analysis. *Musculoskeletal Science and Practice*, *27*, 14–22. https://doi.org/10.1016/j.msksp.2016.11.014

Nicholas, M. K. (2007). The pain self-efficacy questionnaire: Taking pain into account. *European Journal of Pain*, *11*(2), 153–163. https://doi.org/10.1016/j.ejpain.2005.12.008

Oskay, D., Meriç, A., Kirdi, N., Firat, T., Ayhan, Ç., & Leblebicioğlu, G. (2010). Neurodynamic Mobilization in the Conservative Treatment of Cubital Tunnel Syndrome: Long-Term Follow-Up of 7 Cases. *Journal of Manipulative and Physiological Therapeutics*, *33*(2), 156–163. https://doi.org/10.1016/j.jmpt.2009.12.001

Pai, Y. W., Tang, C. L., Lin, C. H., Lin, S. Y., Lee, I. T., & Chang, M. H. (2021). Glycaemic control for painful diabetic peripheral neuropathy is more than fasting plasma glucose and glycated haemoglobin. *Diabetes and Metabolism*, *47*(1). https://doi.org/10.1016/j.diabet.2020.04.004

Parasoglou, P., Rao, S., & Slade, J. M. (2017). Declining Skeletal Muscle Function in Diabetic Peripheral Neuropathy. *Clinical Therapeutics*, *39*(6), 1085–1103. https://doi.org/10.1016/j.clinthera.2017.05.001

Pedler, A. (2010). The pain catastrophising scale. *Journal of Physiotherapy*, *56*(3), 137. https://doi.org/10.1016/s1836-9553(10)70047-3

Peltier, A., Goutman, S. A., & Callaghan, B. C. (2014). Painful diabetic neuropathy. *BMJ (Online)*, *348*(September 2008). https://doi.org/10.1136/bmj.g1799

Petersen, E. A., Stauss, T. G., Scowcroft, J. A., Brooks, E. S., White, J. L., Sills, S. M., Amirdelfan, K., Guirguis, M. N., Xu, J., Yu, C., Nairizi, A., Patterson, D. G., Tsoulfas, K. C., Creamer, M. J., Galan, V., Bundschu, R. H., Paul, C. A., Mehta, N. D., Choi, H., … Mekhail, N. A. (2021). Effect of High-frequency (10-kHz) Spinal Cord Stimulation in Patients with Painful Diabetic Neuropathy: A Randomized Clinical Trial. *JAMA Neurology*, *78*(6), 687–698. https://doi.org/10.1001/jamaneurol.2021.0538

Quattrini, C., Jeziorska, M., Boulton, A. J. M., & Malik, R. a. (2008). Factor Expression and Intra-Epidermal Nerve Fiber Loss in Human Diabetic. *Diabetes Care*, *31*(1), 140–145. https://doi.org/10.2337/dc07-1556.Abbreviations

Ritzwoller, D. P., Ellis, J. L., Korner, E. J., Hartsfield, C. L., & Sadosky, A. (2009). Comorbidities, healthcare service utilization and costs for patients identified with painful DPN in a managed-care setting. *Current Medical Research and Opinion*, *25*(6), 1319–1328. https://doi.org/10.1185/03007990902864749

Rosenberger, D. C., Blechschmidt, V., Timmerman, H., Wolff, A., & Treede, R. D. (2020). Challenges of neuropathic pain: focus on diabetic neuropathy. In *Journal of Neural Transmission* (Vol. 127, Issue 4). Springer Vienna. https://doi.org/10.1007/s00702-020-02145-7

Rosenstock, J., Tuchman, M., Lamoreaux, L., & Sharma, U. (2004). Pregabalin for the treatment of painful diabetic peripheral neuropathy: A double-blind, placebo-controlled trial. *Pain*, *110*(3), 628–638. https://doi.org/10.1016/j.pain.2004.05.001

Sartor, Cristina D., Hasue, R. H., Cacciari, L. P., Butugan, M. K., Watari, R., Pássaro, A. C., Giacomozzi, C., & Sacco, I. C. (2014). Effects of strengthening, stretching and functional training on foot function in patients with diabetic neuropathy: Results of a randomized controlled trial. *BMC Musculoskeletal Disorders*, *15*(1), 1–13. https://doi.org/10.1186/1471-2474-15-137

Sartor, Cristina Dallemole, Watari, R., Pássaro, A. C., Picon, A. P., Hasue, R. H., & Sacco, I. C. N. (2012). Effects of a combined strengthening, stretching and functional training program versus usual-care on gait biomechanics and foot function for diabetic neuropathy: A randomized controlled trial. *BMC Musculoskeletal Disorders*, *13*, 1–10. https://doi.org/10.1186/1471-2474-13-36

Serry, Z. M. H., Mossa, G., Elhabashy, H., Elsayed, S., Elhadidy, R., Azmy, R. M., & Mokhtar, A. (2016). Transcutaneous nerve stimulation versus aerobic exercise in diabetic neuropathy. *Egyptian Journal of Neurology, Psychiatry and Neurosurgery*, *53*(2), 124–129. https://doi.org/10.4103/1110-1083.183449

Shacklock, M. (1995). *Neurodynamics*. *81*(1), 9–16. https://doi.org/https://doi.org/10.1016/S0031-9406(05)67024-1

Shacklock, M. (2005). clinical neurodynamics.A new system of musculoskeletal treatment. In *ELSEVIER*.

Shacklock, M. (2008). Neural mobilization: A systematic review of randomized controlled trials with an analysis of therapeutic efficacy. *Journal of Manual and Manipulative Therapy*, *16*(1), 23–24. https://doi.org/10.1179/106698108790818602

Shahanawaz, S. (2014). Effect of high TENS on neuropathic pain in diabetic neuropathy patients. *Int J Physiother Res*, *2*(4), 604–611.

Sharma, & Maruthy, K. (2019). *Evaluation studies of a new screening device – NEURO TOUCH for screening Diabetic Peripheral Neuropathy*. *4*(6), 7102.

Sharma, S., & Sheth, M. (2017). Effect of neurodynamic mobilization on pain and function in subjects with lumbo-sacral radiculopathy. *Medicine Science | International Medical Journal*,

1. https://doi.org/10.5455/medscience.2017.06.8664

Shashi Kumar, C. G., Maiya, A. G., Manjunath Hande, H., Vidyasagar, S., Rao, K., & Rajagopal, K. V. (2015). Efficacy of low level laser therapy on painful diabetic peripheral neuropathy. *Laser Therapy*, *24*(3), 195–200. https://doi.org/10.5978/islsm.15-OR-12

Shillo, P., Sloan, G., Greig, M., Hunt, L., Selvarajah, D., Elliott, J., Gandhi, R., Wilkinson, I. D., & Tesfaye, S. (2019). Painful and Painless Diabetic Neuropathies: What Is the Difference? *Current Diabetes Reports*, *19*(6). https://doi.org/10.1007/s11892-019-1150-5

Siao, P., & Cros, D. P. (2003). Quantitative sensory testing. *Physical Medicine and Rehabilitation Clinics of North America*, *14*(2), 261–286. https://doi.org/10.1016/S1047-9651(02)00122-5

Singh, P. P., Bindra, S., Singh, S., Aggarwal, R., & Jagmohan, S. (2012). Indian journal of Physiotherapy and occupational therapy. *Indian Journal of Physiotherapy and Occupational Therapy*, *6*(3), 283. http://www.teses.usp.br/teses/disponiveis/27/27148/tde-08102007-211215/publico/Hiperterrorismo_e_midia_na_comunicacao_politica.pdf

Sloan, G., Shillo, P., Selvarajah, D., Wu, J., Wilkinson, I. D., Tracey, I., Anand, P., & Tesfaye, S. (2018). A new look at painful diabetic neuropathy. *Diabetes Research and Clinical Practice*, *144*, 177–191. https://doi.org/10.1016/j.diabres.2018.08.020

Smith, S. C., Lamping, D. L., & Maclaine, G. D. H. (2012). Measuring health-related quality of life in diabetic peripheral neuropathy: A systematic review. *Diabetes Research and Clinical Practice*, *96*(3), 261–270. https://doi.org/10.1016/j.diabres.2011.11.013

Snyder, M. J., Gibbs, L. M., & Lindsay, T. J. (2016). Treating painful diabetic peripheral neuropathy: An update. *American Family Physician*, *94*(3), 227–234.

Spallone, V., & Greco, C. (2013). Painful and painless diabetic neuropathy: One disease or two? *Current Diabetes Reports*, *13*(4), 533–549. https://doi.org/10.1007/s11892-013-0387-7

Staudt, M. D., Prabhala, T., Sheldon, B. L., Quaranta, N., Zakher, M., Bhullar, R., Pilitsis, J. G., & Argoff, C. E. (2020). Current Strategies for the Management of Painful Diabetic Neuropathy. *Journal of Diabetes Science and Technology*. https://doi.org/10.1177/1932296820951829

Talebi, G. A., Saadat, P., Javadian, Y., & Taghipour, M. (2018). Manual therapy in the treatment of carpal tunnel syndrome in diabetic patients: A randomized clinical trial. *Caspian Journal of Internal Medicine*, *9*(3), 283–289. https://doi.org/10.22088/cjim.9.3.283

Tesfaye, S., Boulton, A. J. M., Dyck, P. J., Freeman, R., Horowitz, M., Kempler, P., Lauria, G., Malik, R. A., Spallone, V., Vinik, A., Bernardi, L., Valensi, P., Albers, J. W., Amarenco, G., Anderson, H., Arezzo, J., Backonja, M. M., Biessels, G. J., Bril, V., … Jones, T. (2010). Diabetic neuropathies: Update on definitions, diagnostic criteria, estimation of severity, and treatments. *Diabetes Care*, *33*(10), 2285–2293. https://doi.org/10.2337/dc10-1303

Tesfaye, S., Selvarajah, D., Gandhi, R., Greig, M., Shillo, P., Fang, F., & Wilkinson, I. D. (2016). Diabetic peripheral neuropathy may not be as its name suggests: Evidence from magnetic resonance imaging. *Pain*, *157*, S72–S80. https://doi.org/10.1097/j.pain.0000000000000465

Thakral, G., Kim, P. J., LaFontaine, J., Menzies, R., Najafi, B., & Lavery, L. A. (2013). Electrical stimulation as an adjunctive treatment of painful and sensory diabetic neuropathy. *Journal of Diabetes Science and Technology*, *7*(5), 1202–1209. https://doi.org/10.1177/193229681300700510

Themistocleous, A. C., Ramirez, J. D., Shillo, P. R., Lees, J. G., Selvarajah, D., Orengo, C., Tesfaye, S., Rice, A. S. C., & Bennett, D. L. H. (2016). The Pain in Neuropathy Study (PiNS): A cross-sectional observational study determining the somatosensory phenotype of painful and painless diabetic neuropathy. *Pain*, *157*(5), 1132–1145. https://doi.org/10.1097/j.pain.0000000000000491

Timar, B., Timar, R., Gaiță, L., Oancea, C., Levai, C., & Lungeanu, D. (2016). The impact of diabetic neuropathy on balance and on the risk of falls in patients with type 2 diabetes mellitus: A cross-sectional study. *PLoS ONE*, *11*(4), 1–11. https://doi.org/10.1371/journal.pone.0154654

Truini, A., Spallone, V., Morganti, R., Tamburin, S., Zanette, G., Schenone, A., De Michelis, C., Tugnoli, V., Simioni, V., Manganelli, F., Dubbioso, R., Lauria, G., Lombardi, R., Jann, S., De Toni Franceschini, L., Tesfaye, S., Fiorelli, M., Spagnoli, A., & Cruccu, G. (2018). A cross-sectional study investigating frequency and features of definitely diagnosed diabetic

painful polyneuropathy. *Pain*, *159*(12), 2658–2666. https://doi.org/10.1097/j.pain.0000000000001378

Van Acker, K., Bouhassira, D., De Bacquer, D., Weiss, S., Matthys, K., Raemen, H., Mathieu, C., & Colin, I. M. (2009). Prevalence and impact on quality of life of peripheral neuropathy with or without neuropathic pain in type 1 and type 2 diabetic patients attending hospital outpatients clinics. *Diabetes and Metabolism*, *35*(3), 206–213. https://doi.org/10.1016/j.diabet.2008.11.004

Vileikyte, L., Gonzalez, J. S., Leventhal, H., Peyrot, M. F., Rubin, R. R., Garrow, A., Ulbrecht, J. S., Cavanagh, P. R., & Boulton, A. J. M. (2006). Patient Interpretation of Neuropathy (PIN) questionnaire: An instrument for assessment of cognitive and emotional factors associated with foot self-care. *Diabetes Care*, *29*(12), 2617–2624. https://doi.org/10.2337/dc06-1550

Visser, M., Pahor, M., Taaffe, D. R., Goodpaster, B. H., Simonsick, E. M., Newman, A. B., Nevitt, M., & Harris, T. B. (2002). Relationship of interleukin-6 and tumor necrosis factor-α with muscle mass and muscle strength in elderly men and women: The health ABC study. *Journals of Gerontology - Series A Biological Sciences and Medical Sciences*, *57*(5), 326–332. https://doi.org/10.1093/gerona/57.5.M326

Watanabe, K., Hirano, S., Kojima, K., Nagashima, K., Mukai, H., Sato, T., Takemoto, M., Matsumoto, K., Iimori, T., Isose, S., Omori, S., Shibuya, K., Sekiguchi, Y., Beppu, M., Amino, H., Suichi, T., Yokote, K., Uno, T., Kuwabara, S., & Misawa, S. (2018). Altered cerebral blood flow in the anterior cingulate cortex is associated with neuropathic pain. *Journal of Neurology, Neurosurgery and Psychiatry*, *89*(10), 1082–1087. https://doi.org/10.1136/jnnp-2017-316601

Willems, T., Witvrouw, E., Verstuyftt, J., Vaes, P., & Clercq, D. D. (2002). propioception and muscle strength in subjects with a history of ankle sprains and chronic instability. *Journal of Athletic Training*, *44*(6), 617–623. https://doi.org/10.4085/1062-6050-44.6.617

Win, M. M. T. M., Fukai, K., Nyunt, H. H., & Linn, K. Z. (2020). Hand and foot exercises for diabetic peripheral neuropathy: A randomized controlled trial. *Nursing and Health Sciences*, *22*(2), 416–426. https://doi.org/10.1111/nhs.12676

Xiaohua, G., Dongdong, L., Xiaoting, N., Shuoping, C., Feixia, S., Huajun, Y., Qi, Z., & Zimiao, C. (2021). Severe Vitamin D Deficiency Is Associated With Increased Expression of Inflammatory Cytokines in Painful Diabetic Peripheral Neuropathy. *Frontiers in Nutrition*, *8*(March), 1–8. https://doi.org/10.3389/fnut.2021.612068

Yagihashi, S., Mizukami, H., & Sugimoto, K. (2011). Mechanism of diabetic neuropathy: Where are we now and where to go? *Journal of Diabetes Investigation*, *2*(1), 18–32. https://doi.org/10.1111/j.2040-1124.2010.00070.x

Yang, W., Guo, Z., Yu, Y., Xu, J., & Zhang, L. (2016). Pain Relief and Health-Related Quality-of-Life Improvement After Microsurgical Decompression of Entrapped Peripheral Nerves in Patients With Painful Diabetic Peripheral Neuropathy. *Journal of Foot and Ankle Surgery*, *55*(6), 1185–1189. https://doi.org/10.1053/j.jfas.2016.07.004

Yoo, M., D'Silva, L. J., Martin, K., Sharma, N. K., Pasnoor, M., LeMaster, J. W., & Kluding, P. M. (2015). Pilot Study of Exercise Therapy on Painful Diabetic Peripheral Neuropathy. *Pain Medicine (United States)*, *16*(8), 1482–1489. https://doi.org/10.1111/pme.12743

Young, M. J., Boulton, A. J. M., Macleod, A. F., Williams, D. R. R., & Sonksen, P. H. (1993). Resp Vital Signs.Pdf. *Diabetologia*, *36*, 150–154.

Yovera-Aldana, M., Velasquez-Rimachi, V., Huerta-Rosario, A., More-Yupanqui, M. D., Osores-Flores, M., Espinoza, R., Gil-Olivares, F., Quispe-Nolazco, C., Quea-Velez, F., Moran-Mariños, C., Pinedo-Torres, I., Alva-Diaz, C., & Pacheco-Barrios, K. (2021). Prevalence and incidence of diabetic peripheral neuropathy in Latin America and the Caribbean: A systematic review and metaanalysis. *PLoS ONE*, *16*(5 May), 1–29. https://doi.org/10.1371/journal.pone.0251642

Zhu, G. C., Tsai, K. L., Chen, Y. W., & Hung, C. H. (2018). Original research Neural Mobilization Attenuates Mechanical Allodynia and Decreases Proinflammatory Cytokine Concentrations in Rats With Painful Diabetic Neuropathy. *Ajol.Info*, *98*(5), 1–2. http://www.who.int/mediacentre/

Ziegler, D., Landgraf, R., Lobmann, R., Reiners, K., Rett, K., Schnell, O., & Strom, A. (2018). Painful and painless neuropathies are distinct and largely undiagnosed entities in subjects

participating in an educational initiative (PROTECT study). *Diabetes Research and Clinical Practice*, *139*, 147–154. https://doi.org/10.1016/j.diabres.2018.02.043

Zinman, L. H., Ngo, M., Ng, E. T., Nwe, K. T., Gogov, S., & Bril, V. (2004). Low-Intensity Laser Therapy for Painful Symptoms of Diabetic Sensorimotor Polyneuropathy: A controlled trial. *Diabetes Care*, *27*(4), 921–924. https://doi.org/10.2337/diacare.27.4.921

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